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A new synthesis of 4*H*-1-benzothiopyran-4-ones using (trimethylsilyl)methylenetriphenylphosphorane

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Abstract—The reaction of silyl ester of *S*-acyl(aroyl) thiosalicylic acids **3** with (trimethylsilyl)methylenetriphenylphosphorane **4** in step wise fashion leads to the acylphosphoranes **7**, which subsequently undergo intramolecular Wittig cyclization on the thiolester carbonyl to afford the 4*H*-1-benzothiopyran-4-ones **8** in good to excellent yields.

1. Introduction

1-Benzothiopyran-4-ones are an important class of heterocycles. They serve as key intermediates for the synthesis of biologically active compounds.[1] As part of our ongoing program for developing methodologies via intramolecular Wittig olefination and their subsequent application to biologically useful compounds, the phosphacumulene ylides were envisaged as a versatile reagent offering considerable opportunities for synthetic manipulations.[2] The intramolecular Wittig reaction has been extensively employed as an excellent method for the C–C bond forming process in the synthesis of natural products.[3] In this connection the mono-and bis(trimethylsilyl)methylenetriphenylphosphorane, one of the recent arrivals in the series of organophosphorus reagents, are of special interest.[4] Recently, in our preliminary communication, we have reported a novel method for the synthesis of chromones via intramolecular Wittig reaction using (trimethylsilyl)methylenetriphenylphosphorane.[5] Further, we have studied and extended the scope of this methodology for the construction of benzothiopyran ring.

While chromones (4*H*-1-benzopyran-4-ones) have been extensively investigated regarding their synthesis, their isolation as secondary metabolites, and their potential for broad spectrum biological activity,[6] a little attention has been paid towards the synthesis and biological evaluation of thiochromones (4*H*-1-benzothiopyran-4-ones).[7] These compounds have been prepared and studied for their biological potential, especially as bacteriocides and anticancer agents.[8] In general, 1-benzothiopyran-4-ones are synthesized either by the condensation of a β-keto ester with a thiophenol in polyphosphoric acid[9] or by the cyclization of a β-substituted cinnamate, derived from the constituent thiophenol and an appropriate propiolate.[10] Recently, 4*H*-1-benzothiopyran-4-ones were prepared by the condensation and subsequent acid-induced cyclization of lithiated intermediates derived either from acetoacetanilide,[11] C(α),*N*-benzoylhydrazones or C(α),*N*-carboalkoxy hydrazones[12] with methylthiosalicylate. However, most of these methods suffer either from harsh reaction conditions, poor substituent tolerance or from low chemical yields. Also, some of these methods could not be applied for the synthesis of many target molecules,[13] in particular methoxy-substituted thioflavone.[14] We now report a convenient and efficient route to 1-benzothiopyran-4-ones via intramolecular thiolester carbonyl olefination using (trimethylsilyl) methylenetriphenylphosphorane.

2. Results and discussion

Thiosalicylic acid **1** was converted into its *S*-acyl(aroyl) derivatives **2** by reaction with corresponding acid chloride or anhydride. Compound **2** was then treated with *tert*-butyldimethylsilyl chloride in presence of imidazole to furnish the corresponding silyl ester **3** in good yields. When a mixture of compound **3** and (trimethylsilyl)methylenetriphenylphosphorane[4] **4** was heated in refluxing THF, the desired 2-substituted, 4*H*-1-benzothiopyran-4-ones **8** were obtained in 58–90% yields (Table 1). The conversion of **3** into **8** could be explained by a sequence of reaction as depicted in Scheme 1. The plausible mechanism can be visualized as initial acylation of (trimethylsilyl)methylenetriphenylphosphorane **4** by **3** to the resulting phosphonium salt **5**. There is then migration of the trimethylsilyl group from C to O followed by the extrusion of silyl ether **6** leading to the acylphosphorane **7**, which subsequently undergoes ring closure via the intramolecular Wittig

Keywords: *S*-acyl(aroy)thiosalicylic acids; (trimethylsilyl)methylenetriphenylphosporane; acylphosphorane; intramolecular Wittig cyclization; thiochromones.

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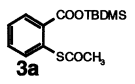
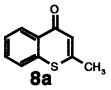
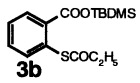
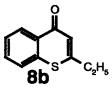
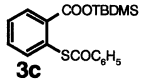
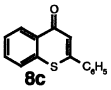
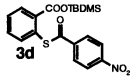
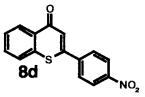
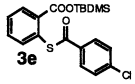
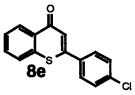
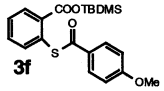
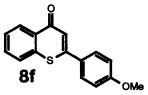
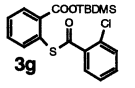
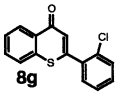
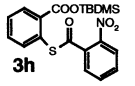
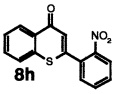
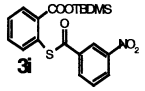
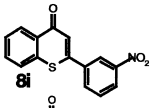
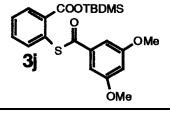
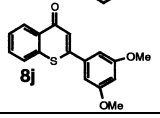
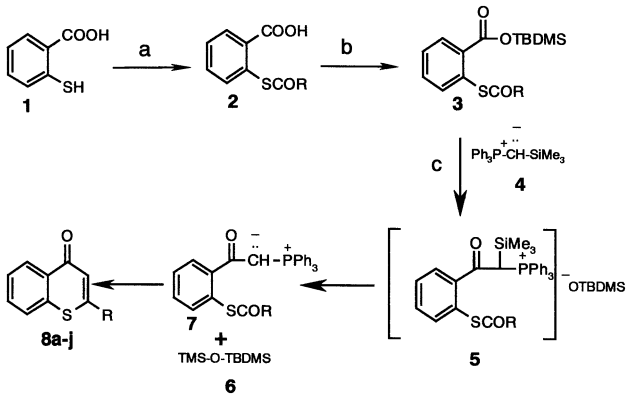
Table 1. One-pot synthesis of 2-substituted, 4*H*-1-benzothiopyran-4-ones from **3** and **4**

No.	Substrate	Product[a]	R.T (h)	Yield (%)[b]
1	 **3a**	 **8a**	16	80
2	 **3b**	 **8b**	17	76
3	 **3c**	 **8c**	18	90
4	 **3d**	 **8d**	22	68
5	 **3e**	 **8e**	21	69
6	 **3f**	 **8f**	25	60
7	 **3g**	 **8g**	35	62
8	 **3h**	 **8h**	38	63
9	 **3i**	 **8i**	30	65
10	 **3j**	 **8j**	33	58

[a] All products were characterized by their satisfactory spectroscopic data.
[b] Yields refer to isolated pure products.

reaction on the thiolester carbonyl to afford the desired thiochromones **8**.

With a view to ascertaining the reaction pathway, the reaction of the silyl ester of *S*-acetylthiosalicylic acid **3a** with **4** was carried out at different temperature in order to trap the intermediates formed during reaction. Although the treatment of **3a** with **4** in THF at room temperature did not show any progress of reaction, the extrusion of silyl ether **6** and formation of the acylphosphorane **7a** could be observed when the reaction was performed at higher temperature (55°C). Interestingly, the acylphosphorane **7a** was found to be stable enough to be isolated and was further characterized by its satisfactory IR, ^{1}H NMR and MS spectroscopic data. Compound **7a** on heating in refluxing THF gave the desired 2-methyl-1-benzothiopyran-4-one (**8a**). The phosphonium salt **5a** could not be isolated presumably due to its fast rearrangement into the acylphosphorane **7a**. However, the above finding indicates that compound **7a** which results from **5a** after the cleavage of silyl ether **6**, is one of the intermediates which undergoes subsequent



Scheme 1. *Reagents and conditions*: (a) RCOCl or $(RCO)_2O$, aq. KOH, 0°C–room temperature, 0.5 h, 75–80%; (b) TBDMS-Cl, imidazole (1.5 equiv.), CH_2Cl_2, 0°C–room temperature, 7–8 h, 65–70%; (c) 16–38 h in THF, reflux, 58–90%.

intramolecular Wittig cyclization at reflux temperature to afford the desired product **8a**.

The intramolecular Wittig cyclization involving phosphorus ylide and thiolester carbonyl is general for the preparation of a variety of thiochromone derivatives. Further, an electron donating substituent in **3f** reduces the rate of intramolecular Wittig reaction (Table 1, entry 6) and hence a little longer time is required to complete the reaction affording relatively low yield of the product **8f**. As it can be seen from Table 1, the steric effect during the Wittig cyclization resulting from the substitution in aroyl group appears to be more significant than the electronic factor. Thus, an *ortho*-substituent such as the chloro and nitro group in **3g** and **3h**, respectively and *meta*-substituents such as the nitro and methoxy group in **3i** and **3j** have pronounced steric hindrance due to their close proximity to the carbonyl group and hence a longer time is required to complete the reaction affording relatively low yields of products **8g–j** (Table 1, entries 7–10). It may be mentioned that the cyclization of cinnamate with an electron donating substituent such as methoxy by a usual process led to the formation of the corresponding coumarin instead of thiochromone.[14] Also, the reaction of methoxy substituted benzenethiol with ethylbenzoylacetate by a conventional method has been found to give a mixture of the corresponding thioflavone and isomeric thiocoumarin or only the thiocoumarin in very low yield.[15] In this connection, the present methodology for **8f** and **8j** is noteworthy. Some of the synthesized compounds are precursors for thiochroman-4-ones, which serve as key intermediates in the syntheses of a variety of compounds of biological interest.[16]

3. Conclusion

In summary, we have developed an efficient annulation protocol for a variety of thiochromones via intramolecular Wittig thiolester carbonyl olefination using (trimethylsilyl)-methylenetriphenylphosphorane. This method offers a more general and one-pot synthesis of 1-benzothiopyran-4-one. The protocol developed could be useful particularly in the synthesis of methoxy-substituted benzothiopyranones. Further investigations to explore the synthetic potential of

mono- and bis-silylated phosphorus ylides are currently underway in our laboratories.

4. Experimental

4.1. General information

The solvents were purified by standard procedures before use; petroleum ether of boiling range 60–80°C was used. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on an ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker AC-200 NMR spectrometer. The chemical shifts are reported in parts per million (δ) with tetramethyl silane as an internal standard. Mass spectra were obtained with a Finnigan MAT-1020B-70 eV mass spectrometer. Elemental analyses were carried on a Carlo Erba CHNS-O analyzer.

4.2. Procedure for *S*-acyl(aroyl)thiosalicylic acid (2)

10 g of ice followed by freshly distilled acid chloride or acid anhydride (10 mmol) were added to an ice-cold solution of thiosalicylic acid **1** (8 mmol) and potassium hydroxide (20 mmol) in water (12 ml). The resulting mixture was stirred vigorously for 0.5 h at room temperature. After the reaction was complete, the solution was acidified with dil. HCl and the material, which precipitated out, was filtered and washed with water. Recrystallization of the crude product from pet. ether/ethyl acetate or hexane gave the product **2** in 75–80% yield.

4.3. Procedure for *tert*-butyldimethylsilyl ester of *S*-acyl(aroyl)thiosalicylic acid (3)

A solution of compound **2** (10 mmol) and imidazole (15 mmol) in dichloromethane (5 ml) was cooled to 0°C, and mixture was stirred under nitrogen atmosphere. To the above solution, was added *tert*-butyldimethylsilyl chloride (13 mmol) at 0°C and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 7–8 h. After the reaction was complete, the reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the product **3** in 65–70% yield, which was used as such for the next reaction without further purification.

4.4. Preparation of 4

The (trimethylsilyl)methylene triphenyl phosphorane (**4**) was prepared following the literature procedure[4] from methylenetriphenylphosphorane and trimethylsilyl chloride.

4.5. Procedure for the preparation of 7a

To a solution of **3a** (1 g, 3.25 mmol) dissolved in absolute THF (5 ml) was added an equimolar amount of silylated ylide **4** (1.325 g, 3.25 mmol) in THF (5 ml). The reaction mixture was heated at 55°C for 8 h. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure and residue thus obtained was washed several times with petroleum ether to afford 1.25 g (85%) of sufficiently pure acylphosphorane **7a**, which was fully characterized by spectroscopic and analytical data.

4.5.1. Compound 7a. Oil; IR ν_{max}/cm^{-1} ($CHCl_3$): 1294, 1437, 1480, 1540, 1610, 1705; ^{1}H NMR ($CDCl_3$) δ: 0.89 (s, 3H), 2.04 (d, 1H, J=14 Hz), 7.27–7.77 (m, 19H). Mass (EI), *m/z* (%): M$^+$ 454 (1), 440 (1), 277 (10), 224 (3), 215 (40), 201 (78), 152 (35), 107 (25), 75 (100). Anal. Calcd for $C_{28}H_{23}O_2PS$: C, 74.00; H, 5.10; S 7.04. Found C, 73. 76; H, 5.34; S, 7.34.

4.6. Procedure for the preparation of 4*H*-1-benzothiopyran-4-ones (8)

To a solution of compound **3** (50 mmol) in absolute THF (5 ml) was added under stirring the equimolar amount of silylated ylide **4** (50 mmol) in THF (5 ml). The reaction mixture was refluxed for the indicated length of time (Table 1). The reaction was monitored by TLC. After completion of reaction, the solvent was evaporated and the residue was purified by column chromatography (pet. ether/ethyl acetate, 98:2), to afford the product **8**, in 58–90% yields.

4.6.1. 2-Methyl-4*H*-1-benzothiopyran-4-one (8a). Colorless solid; mp 100–101°C (Lit.[9] 103°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1400, 1600, 1703; ^{1}H NMR ($CDCl_3$) δ: 2.48 (s, 3H), 6.85 (s, 1H), 7.55–7.65 (m, 3H), 8.09–8.39 (m, 1H). Mass (EI), *m/z* (%): M$^+$ 176 (100), 147 (85), 136 (87).

4.6.2. 2-Ethyl-4*H*-1-benzothiopyran-4-one (8b). Oil; IR ν_{max}/cm^{-1} ($CHCl_3$): 1676; ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, J=8 Hz), 2.62 (q, 2H, J=8 Hz), 6.9 (s, 1H), 7.32–7.52 (m, 3H), 7.6–8.0 (m, 1H). Mass (EI), *m/z* (%): M$^+$ 190 (20), 167 (40), 149 (100), 136 (35). Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85. Found C, 69.68; H, 5.57; S, 17.13.

4.6.3. 2-Phenyl-4*H*-1-benzothiopyran-4-one (8c). Colorless solid; mp 126°C (Lit.[10a] 122–123°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1600, 1688 1445; ^{1}H NMR ($CDCl_3$) δ: 7.12 (s, 1H), 7.49–7.67 (m, 6H), 8.03–8.07 (m, 3H). Mass (EI), *m/z* (%): M$^+$ 238 (40), 215 (100), 136 (50), 107 (60), 77 (45).

4.6.4. 2-(4′-Nitrophenyl)-4*H*-1-benzothiopyran-4-one (8d). Colorless solid; mp 252°C (Lit.[17] 250–252°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1690, 1532, 1215; ^{1}H NMR ($CDCl_3$) δ: 6.92–7.05 (m, 3H), 7.51–7.58 (m, 2H), 7.93–8.33 (m, 4H). Mass (EI), *m/z* (%): M$^+$ 283 (40).

4.6.5. 2-(4′-Chlorophenyl)-4*H*-1-benzothiopyran-4-one (8e). Colorless solid; mp 187–189°C (Lit.[13] 189–190°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1692, 1540, 1215; ^{1}H NMR ($CDCl_3$) δ: 7.21–7.50 (m, 5H), 7.84–7.97 (m, 4H). Mass (EI), *m/z* (%): M$^+$ 272 (30), 244 (35), 139 (100).

4.6.6. 2-(4′-Methoxyphenyl)-4*H*-1-benzothiopyran-4-one (8f). Colorless solid; mp 126–127°C (Lit.[12] 126–127°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1666, 1540, 1243; ^{1}H NMR ($CDCl_3$) δ: 3.90 (s, 3H), 6.9–7.03 (m, 5H), 7.5–7.56 (m, 2H), 7.94 (d,

1H, J=4 Hz), 8.08 (d, 1H, J=6 Hz). Mass (EI), m/z (%): M^+ 268 (80), 240 (40), 225 (22).

4.6.7. 2-(2′-Chlorophenyl)-4*H*-1-benzothiopyran-4-one (8g). Colorless solid; mp 201°C (Lit.[18] 204°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1694, 1213; ^{1}H NMR ($CDCl_3$) δ: 6.95–7.00 (m, 1H), 7.44–7.9 (m, 4H), 8.11–8.15 (m, 4H). Mass (EI), m/z (%): M^+ 272 (35), 244 (28), 139 (95).

4.6.8. 2-(2′-Nitrophenyl)-4*H*-1-benzothiopyran-4-one (8h). Colorless solid; mp 284°C (Lit.[18] 282°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1694, 1540, 1224; ^{1}H NMR ($CDCl_3$) δ: 6.89–7.04 (m, 2H), 7.43–7.57 (m, 4H), 7.91–8.09 (m, 3H). Mass (EI), m/z (%): M^+ 283 (80), 139 (76), 123 (38).

4.6.9. 2-(3′-Nitrophenyl)-4*H*-1-benzothiopyran-4-one (8i).[19] Colorless solid; mp 215–216°C; IR ν_{max}/cm^{-1} ($CHCl_3$): 1692, 1530, 1243; ^{1}H NMR ($CDCl_3$) δ: 6.9–7.1 (m, 3H), 7.48–8.01 (m, 6H). Mass (EI), m/z (%): M^+ 283 (80), 139 (95), 123 (25). Anal. Calcd for $C_{15}H_9NO_3S$: C, 63.59; H, 3.20; N, 4.94; S, 11.32. Found C, 63.40; H, 3.52; N, 5.14; S, 11.60.

4.6.10. 2-(3′,5′-Dimethoxyphenyl)-4*H*-1-benzothiopyran-4-one (8j). Colorless solid; mp 234–236°C (Lit.[13] 236°C); IR ν_{max}/cm^{-1} ($CHCl_3$): 1686, 1534, 1215; ^{1}H NMR ($CDCl_3$) δ: 3.9 (s, 6H), 7.25–7.42 (m, 4H), 7.87–8.09 (m, 4H). Mass (EI), m/z (%): M^+ 298 (80), 137 (85), 139 (88), 77 (38).

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